Phenoxymethyl Penicillin in the Horse: An Alternative to Parenteral Administration of Penicillin

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ABSTRACT

This preliminary study evaluated phenoxymethyl penicillin (Penicillin V) as an alternative to parenteral administration of penicillin in horses. Penicillin V was administered orally to five horses at two different doses and plasma levels of the drug were determined at timed intervals. The results were evaluated by regression analysis. Following the administration of penicillin V at a dose of 66,000 IU/kg or 110,000 IU/kg, the mean peak plasma levels obtained were 1.55 μg/mL and 2.34 μg/mL respectively. A plasma level two to four times above the minimal inhibitory concentration level of *Streptococcus equi* and *Streptococcus zooepidemicus* was maintained for 325 minutes at 66,000 IU/kg and 349 minutes at 110,000 IU/kg. Penicillin V given orally was thus shown to be an acceptable alternative to parenteral administration of penicillin in the horse.

Key words: Penicillin V, oral, horse.

RÉSUMÉ

Cette étude préliminaire visait à déterminer la valeur de l'administration buccale de phénoxyméthylpénicilline, ou pénicilline V, comme alternative à l'injection parentérale de pénicilline, chez les chevaux. Les auteurs administrèrent donc deux doses de pénicilline V, par la voie buccale, à cinq chevaux; ils déterminèrent ensuite les teneurs plasmatiques de l'antibiotique, à intervalles précis, et évaluèrent leurs résultats par l'analyse de régression. Après l'administration buccale de pénicilline V, à raison de 66 000 ou 110 000 UI/kg, la concentration plasmatique moyenne la plus élevée atteignit respectivement 1,55 et 2,34 μg/mL. Une concentration plasmatique de deux à quatre fois supérieure à la concentration inhibitrice minimale de *Streptococcus equi* et *Streptococcus zooepidemicus* dura respectivement 325 et 349 minutes, selon que la dose était de 66 000 ou 110 000 UI/kg. L'administration buccale de pénicilline V s'est par conséquent avérée une alternative acceptable à l'injection parentérale de pénicilline, chez le cheval.

Mots clés: pénicilline V, voie buccale, cheval.

INTRODUCTION

The penicillins are the oldest of the antibiotic group of drugs (1). However, a major shortcoming with their use in the horse is the lack of an established penicillin preparation that can be administered orally for long-term treatment of chronic infections such as abdominal abscesses or bacterial bronchitis. Procaine penicillin G, alone or in association, is the most widely used preparation in the horse (2). However, certain adverse reactions have been associated with its use: hyperethesia (1), excitation (2), muscular soreness (2), anaphylactic reaction (2) and abscess formation at injection sites. In addition, some horses are "needleshy", making repeated administration difficult. Potassium benzyl penicillin, another penicillin preparation, has been related to a transient cardiac arrest in a foal (3).

Oral administration of penicillin would eliminate many of the complications associated with the injectable form. Phenoxymethyl penicillin (Penicillin V) is prepared by biosynthesis and, unlike penicillin G, has been shown to be stable at a pH range below 5 (4). This acid stability prevents penicillin V from being destroyed by the gastric juice and, therefore in man, plasma concentration two to five times higher can be obtained than an equivalent oral-dose basis of penicillin G (4). The spectrum of activity of penicillin V is very similar to that of penicillin G (4). Following the enteral administration of penicillin V therapeutic penicillin V therapeutic blood levels have been obtained in swine (5), dogs (5, 6), poultry (5) and man (6). In the

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only study evaluating oral penicillin V in horses, therapeutic blood levels were not obtained (5). However, the highest dosage evaluated was 12,331 IU/kg of body weight (5).

The purpose of this present study was to determine the plasma concentrations following oral administration of large doses of penicillin V to horses in order to determine if this would be a feasible approach to penicillin therapy in this species.

MATERIALS AND METHODS

Six adult horses (four mares, two geldings) in good physical condition were used. Phenoxymethyl penicillin free acid in a powder form (Penicillin V; Powder, Upjohn Company, Kalamazoo, Michigan) was mixed with water and was administered as a single dose via stomach tube one hour before the morning feeding. Dose A (66,000 IU/kg) and dose B (110,000 IU/kg) of penicillin V were given two weeks apart. The mean body weight (±SD) of the horses at the time of the study was 518.8 ± 35.9 kg.

Following administration of each dose, blood samples were obtained by jugular venipuncture using aseptic technique at zero, 15, 25, 35, 60 and 90 minutes and three, six, eight, 12 and 24 hours. The plasma was removed and refrigerated. All assays were performed within 24 hours of collection. Bioassays for levels of penicillin V in plasma were performed by means of a disk agar diffusion method (7). Samples and standards were tested on plates in triplicate using *Micrococcus lutea* as the test organism. The plates were incubated at 35°C for 16 hours and the concentration of penicillin V in each sample was determined by measuring the zones of inhibition. A standard curve was made up for each assay and the results of the sample disks were read against this curve which was always linear with a coefficient of correlation of at least 0.93.

Two horses had a severe laminitis episode following administration of penicillin V and were not given the drug subsequently. Therefore data was obtained in five horses for each of the two doses administered.

TABLE I. Mean Plasma Concentrations of Penicillin V Following Oral Administration at Two Dosage Levels in the Horse (μg/mL)

Time (h)	Dosage of Penicillin V 66,000 IU/kg	110,000 IU/kg
0	0	0
0.25	1.40 ± 0.17	0.68 ± 0.05
0.41	1.26 ± 0.36	1.62 ± 0.31
0.58	1.38 ± 0.11	1.55 ± 0.78
1.0	1.18 ± 0.03	1.86 ± 0.26
1.5	0.83 ± 0.03	1.11 ± 0.18
3.0	0.30 ± 0.02	0.58 ± 0.08
6.0	0.11 ± 0.004	0.13 ± 0.002
8.0	0.03 ± 0.001	0.14 ± 0.004
12.0	N.M.	0.06 ± 0.001
24.0	N.M.	N.M.

N.M. = Not measurable levels of penicillin V

The relationship between penicillin V level (P) and time was evaluated by standard regression analysis (8). Nonlinearity of the regression curves was corrected by reexpressing the variables: the square root of the sum of the penicillin V plasma concentration plus one was plotted against the logarithm of the time in minutes (9, 10).

RESULTS

The mean plasma concentrations of penicillin V at various time intervals following the two doses of this drug are shown in Table I. The peak values were obtained within the first hour after administration for both doses. The mean peak plasma concentrations of penicillin V following administration of 66,000 IU/kg and 110,000 IU/kg were 1.55 μg/mL and 2.34 μg/mL, respectively.

Regression analysis of the plasma concentrations for both doses plotted against time (60 to 360 minutes) yielded the lines shown in Figs. 1 and 2. In both cases the regression coefficient was highly significant ($P < 0.001$). The estimated time for the plasma concentrations to fall to 0.10 μg/mL within the 95% confidence limits were 325 minutes (178,633) and 349 minutes (160,853) for dose A and dose B, respectively.

DISCUSSION

The early peak in plasma concentration indicates that penicillin V is absorbed rapidly following

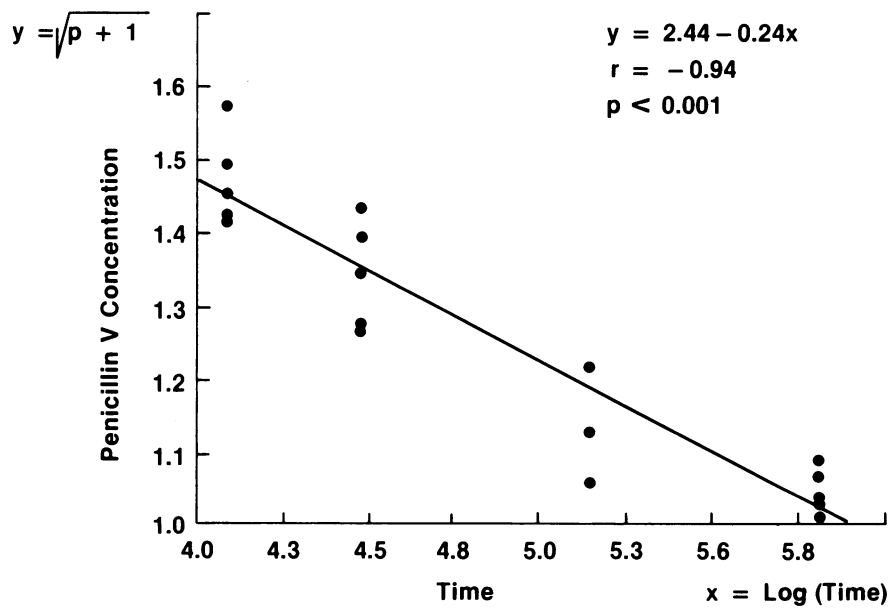

Fig. 1. Mean plasma concentrations of penicillin V in five horses following oral administration of 66,000 IU/kg. Regression line is shown. Plasma concentration (μg/mL) is expressed as the square root of the sum plasma concentration plus one and time (60-360 minutes) is expressed logarithmically. The 180 minute plates (third series) of horses 3 and 4 could not be read and were excluded from the evaluation.

oral administration in horses. The mean peak plasma concentrations obtained at the dose of 66,000 IU/kg (1.55 μg/mL) and 110,000 IU/kg (2.34 μg/mL) are similar to mean peak serum concentrations observed in dogs (1.3-2.1 μg/mL) (5, 6, 11) following administration of penicillin V at therapeutic doses (14,000-16,960 IU/kg). In adult humans, following treatment of 400,000 IU, the mean serum penicillin V level, one hour posttreatment, ranges from 1.06-1.10 μg/mL (12, 13). This is comparable to the mean plasma concentration of 1.18 μg/mL obtained at 66,000 IU/kg. The minimal inhibitory concentration (MIC) of bacteria highly sensitive to penicillin is 0.03 μg/mL (14). The plasma concentrations of penicillin required for bactericidal activity is two to four times the MIC (14). Thus, blood levels of approximately 0.10 μg/mL are necessary to ensure effectiveness. Our experimental data indicated that a dose of 66,000 IU/kg would provide plasma levels of penicillin V above or equal to 0.10 μg/mL for 325 minutes. This plasma level should be effective against *Streptococcus equi*, *Streptococcus zooepidemicus*, *Streptococcus* (G P.A.) and *Staphylococcus aureus* (14). It seems reasonable that penicillin V administered at a dosage of 66,000 IU/kg every six hours would provide adequate therapeutic levels of the drug. A problem with this schedule of therapy is that between each dose administration there is a period during which the antibiotic plasma level is below the MIC. However, it had been suggested that because of residual inhibitory effect, levels above the required MIC are not essential for the penicillins to provide continued bactericidal activity (1, 15, 16). This may not apply to critically ill horses with weakened host defense mechanisms; more frequent administration to maintain continuous penicillin V levels above the MIC may be necessary.

The presence of gastric ingesta may influence the absorption of penicillin V in man and the dog (4, 13). While this effect was not evaluated in the present study, our results indicated satisfactory absorption was obtained following oral administration of the drug before the morning feeding. This suggests that penicillin V be administered prior to feeding.

In the current study, two horses suffered acute laminitis 24-36 hours after a single dose of penicillin V. However, two other animals on the research farm which were not administered penicillin V also had acute episodes of laminitis. Since then 40 horses (including two horses treated for two months) have been treated with penicillin V orally with no laminitis episode. Therefore, we feel that the two cases of laminitis were unlikely to have resulted from the administration of penicillin V. In two of these 40 horses, transient diarrhea developed but it responded to discontinuation of penicillin V therapy.

On the basis of our study, we conclude that penicillin V can be used as an efficient antimicrobial agent in horses. However, investigation leading to a suitable formulation of an oral preparation (i.e. paste) is needed. The advantage of an oral form of the drug would make long-term treatment with penicillin easier for both the owner and the horse.

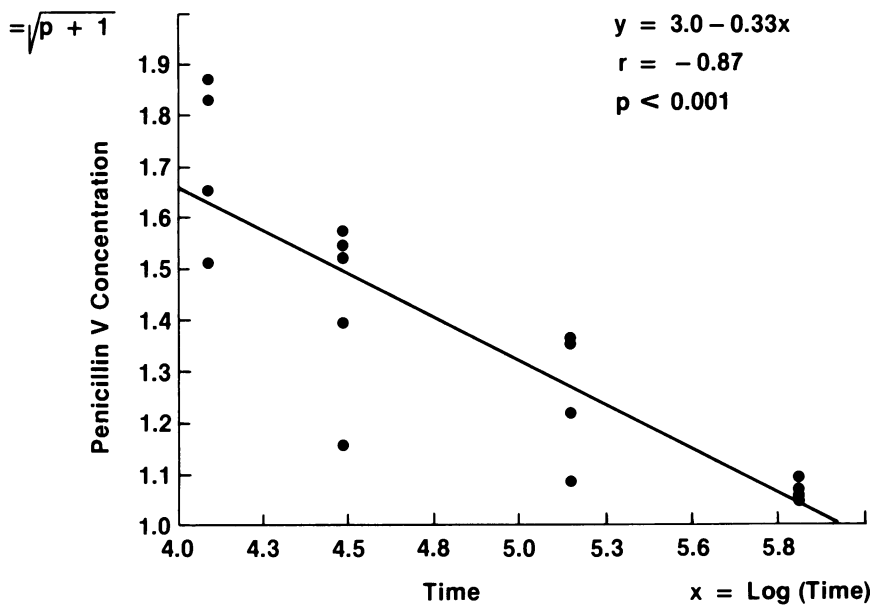

Fig. 2. Mean plasma concentrations of penicillin V in five horses following oral administration of 110,000 IU/kg. Regression line is shown. Plasma concentration (μg/mL) is expressed as the square root of the sum plasma concentration plus one and time (60-360 minutes) is expressed logarithmically. The 180 minute plates (third series) of horse 3 could not be read and were excluded from the evaluation. In the first and fourth series, two dots are superimposed.

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